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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

SPIEGLER, ALEXANDER H

ART UNIT

PAPER NUMBER

1637

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application N .

09/613,535

Applicant(s)

MURPHY ET AL.

Examiner

Alexander H. Spiegler

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 February 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7,9-19 and 21-57 is/are pending in the application.
- 4a) Of the above claim(s) 49-52 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7,9-19,21-48 and 53-57 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

1. This action is in response to Paper No. 13, filed on February 18, 2003. Currently, claims 1-7, 9-19 and 21-57 are pending; claims 1-7, 9-19, 21-48 and 53-57 have been examined on the merits, and claims 49-52 have been withdrawn.

2. This action contains new rejections, not necessitated by amendment, and therefore, this action is made NON-FINAL. The previous rejections of Paper No. 12 (Office Action mailed on 11/19/02) are hereby withdrawn. Applicants inclusion of a clean copy of the pending claims is appreciated.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 7, 17, 34, 37-48 and 53-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 7 and 17 are indefinite because it is not clear as to whether a the chain-terminating agent is added at all. Given the interpretation wherein only one chain-terminating agent is added in step f) of claims 1 and 9, it would then appear as if claims 7 and 17, respectively, which are “performed without the addition of a chain-terminating agent” would nullify the addition of a chain-terminating agent. Applicants should clarify whether claims 7 and 17 eliminate step f) from claims 1 and 9, respectively.

B) Claim 34 is indefinite because it is not clear that this claim is further limiting from

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claim 9, because the first extended nucleic acid of claim 9, would necessarily comprise the primer.

C) Claims 37-48 and 53-57 over “length-altering agent” because it is not clear as to what is meant by this recitation.

MPEP 2173.02 discusses 35 U.S.C. 112, 2nd paragraph:

The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:

- (A) The content of the particular application disclosure;
- (B) The teachings of the prior art; and
- (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph. See, e.g., *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000)... If the scope of the invention sought to be patented cannot be determined from the language of the claims with a reasonable degree of certainty, a rejection of the claims under 35 U.S.C. 112, second paragraph is appropriate. *In re Wiggins*, 488 F.2d 538, 179 USPQ 421 (CCPA 1973).

In the instant case, the recitation of “length-altering agent” is not found in any patent or pre-patent publication, nor is this recitation defined in the specification. The specification lists some examples of what is encompassed by this recitation (see pgs. 9-10 and 38). Thus, the specification, at best, teaches examples of what *might* be encompassed by the recitation of “length-altering agent”, but does not specifically define what “length-altering agent” means. Accordingly, the prior art, specification and the claims fail to set out and circumscribe “length-altering agent” with a reasonable degree of clarity and particularity.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 7 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Arnold et al. (USPN 6,153,410).

Claims 7 and 17 are drawn to an in vitro recombination method using a defined primer, wherein there is no step of adding a chain-terminating agent. That is, given the broadest reasonable interpretation, if claim 1 (and claim 9) only adds one chain-terminating agent, and claims 7 (and 17) “is performed without the addition of a chain-terminating agent”, then the claims are directed to an in vitro recombination method using a defined primer, and not adding any chain-terminating agents.

Arnold teaches such an in vitro recombination method comprising using a defined primer without the addition of a chain-terminating agent (see cols. 3-10, 16-17, and 41-42).

7. Claims 1-7, 9-17, 19, 21-39, 43-44, 46, 48-53 and 55-57 are rejected under 35 U.S.C. 102(b) as being anticipated by Short et al. (WO 98/01581, cited in the IDS).

Short teaches a method creating a nucleic acid comprising;

a) annealing a defined primer nucleic acid to at least one template nucleic acid;

b) performing a first extension by extending the primer nucleic acid employing the

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template nucleic acid to form an extended nucleic acid;

c) denaturing the extended nucleic acid from the template nucleic acid;

d) annealing the extended nucleic acid to at least a second template nucleic acid;

e) performing a second extension by extending the extended nucleic acid employing the second template nucleic acid to form a twice extended nucleic acid;

f) adding at least one chain terminating agent (i.e. a chain terminator), before or during at least one of the first or second extension, wherein said chain-terminating agent is incorporated into said extended nucleic acid (pgs. 8-9).

The reference is directed to producing polynucleotides by interrupting polynucleotide synthesis using a chain terminator, followed by specific, self-primed primer extension (see pgs. 7 and 67). The first step, interrupting polynucleotide synthesis, encompasses both random and non-random primer extension because Short does not limit the polynucleotide synthesis to only random amplification (see pgs. 7 and 67). During the interrupting step, fragments of different length of the polynucleotide are being generated, creating "resultant polynucleotides" (pg. 7). Following the interrupting step, single or double stranded polynucleotides are added to the resultant polynucleotide fragments, wherein the added polynucleotides comprise an "area of identity in an area of heterology" to one or more of the resultant polynucleotide fragments (i.e., these added polynucleotides are of a defined sequence, and will anneal to a defined region) (pg. 7). Following the annealing of the defined polynucleotides (i.e., defined primer), the polynucleotides are incubated, thus performing linear primer extension.

Thus, Short teaches that the addition of a chain terminator occurs **before** the annealing of a defined primer nucleic acid to at least one first template nucleic acid. However, it is also

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inherent that while some of the added polynucleotides (i.e., defined primers) are annealing to some resultant polynucleotides, some of the resultant polynucleotides are simultaneously are still being generated addition of chain terminators. That is, since some of the resultant fragments will be small, they will be generated more quickly, and therefore, will begin annealing to the added polynucleotides, while some of the larger resultant fragments are still being generated interrupted by the chain terminators. Thus, Short also teaches that the addition of the chain terminator also occurs **during** the at least one of the first extension (i.e., **during** the annealing of the

It is also noted that steps c)-e) can be occur a plurality of times to produce a polynucleotide that encodes a protein of interest (pgs. 6-7). The reference also teaches the various possibilities of the polynucleotides (e.g. lengths of polynucleotides) used, amplification conditions, etc. (pgs. 27-35). The reference also teaches polynucleotide synthesis can be interrupted by polymerase inhibitors, DNA binding proteins, etc. (pg. 67). Furthermore, the reference teaches that if further processing of the resultant polynucleotides is desired, DNA adducts (and thus, any of the agents added interrupted polynucleotide synthesis) must be removed (pg. 8).

Response to Applicants Arguments

Applicants argue that the claimed invention is drawn to non-random primer extension, whereas the reference teaches only random primer extension. This argument is not persuasive for several reasons. First, the teachings of Short do not limit his teachings to only random primer extension. Even assuming that Short teaches random primer extension in his first step, he clearly teach non-random primer extension when the added polynucleotides anneal to the resultant

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polynucleotides. That is, the added polynucleotides act as defined primers, as they anneal to specific resultant polynucleotides. Since the claims are drawn to adding the chain terminators **before** the annealing of the defined primer, even if Short teaches an initial random primer extension step (with the addition of the chain terminators), it still occurs **before** the annealing of the defined primers.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. Claims 18, 45 and 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Short et al. (WO 98/01581, cited in the IDS), as applied to claims 1-7, 9-17, 19, 21-39, 43-44, 46, 48-53 and 55-57 above, and in view of Rosenthal (USPN 6,087,095).

The teachings of Short are presented above. Specifically, Short teaches an in vitro recombination method using a defined primer, wherein a chain terminator is added. Short teaches the chain terminating agent can be removed by heat (pg. 8). Short does not teach the modifying or removing of the chain-terminating agent using an exonuclease; or using a chemical treatment, such as the Maxam and Gilbert treatment as a length-altering agent.

However, Rosenthal teaches that if additional cycles of extension are to be performed, Exonuclease III can be added to remove a chain terminator (col. 5-6). Rosenthal also teaches that preferred chain terminators are dideoxynucleotides (col. 5). Rosenthal also teaches that a

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Maxam Gilbert treatment can be used as a length-altering agent (col. 1), as well as phosphorothioate (col. 6-7 and Examples 1-9).

In view of the teachings of Rosenthal, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Short so as to have removed the chain terminators (using exonuclease), in order to have achieved the benefit of providing additional cycles of nucleic acid extension for producing a plurality of polynucleotides that encode a polypeptide of interest. Additionally, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a Maxam-Gilbert treatment as a length-altering agent, in order to have achieved the benefit of interrupting the polynucleotide synthesis of smaller polynucleotides.

10. Claims 40-42 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Short et al. (WO 98/01581, cited in the IDS), as applied to claims 11-7, 9-17, 19, 21-39, 43-44, 46, 48-53 and 55-57 above, and in view of Laney et al. (USPN 5,679,512).

The teachings of Short are presented above. The reference does not teach the incorporation of a ribonucleotide into the extension product.

However, Laney (col. 11) teaches that it is well known to have used polynucleotide primers comprising modified nucleotides at the 3' end of the polynucleotide primer (i.e. that would be incorporated into an extension product), said modified nucleotides comprising, phosphorothioates, methylated bases, and ribonucleotides.

In view of the teachings of Laney, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of Recombinant Biocatalysts and Rosenthal so as to have included the steps of incorporating

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modified bases into the 3' end of a polynucleotide primer, in order to have achieved the benefits of amplifying a plurality of alternative templates.

Conclusion

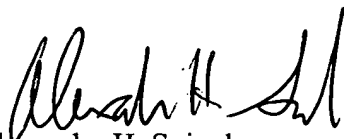
11. No claims are allowable.


Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (703) 305-0806. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014. Applicant is also invited to contact the TC 1600 Customer Service Hotline at (703) 308-0198.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


Alexander H. Spiegler
May 29, 2003


KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

6/2/03